

Applicants respectfully disagree, because the general disclosure and specific examples provided in the specification fully describe and teach the claimed invention in its totality for at least the following reasons.

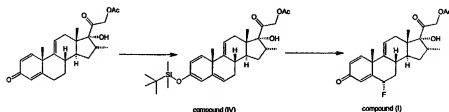
The above referenced application relates in general to a process of introducing a fluorine in the position 6a in Marcus-type compound of the steroid having plurality of the substituents of the C and D rings, in order to obtain the compound of formula (I), which is useful for obtaining steroids having therapeutic application as anti-inflammatory and anti-asthmatic agents. An important aspect of the process is the step of introducing fluorine in the 6th position of the steroid without affecting the epoxy functionality of the C ring. According to the disclosure of the application, the diastereoselectivity may only be obtained by using a stable silyl enol ether, such as that in the silyl derivatives of formula (IV), which withstands the fluorination conditions without breaking until the fluorine atom has been introduced, and by using a gentle enough fluorine reagent, such as the N-fluorosulfonimide- or N-fluorosulfonamide type fluorinating agent, so that the silyl derivative does not break before introducing the fluorine. As illustrated in the reference examples of the application, other combinations, such as enol ethers and fluorine reagents, or silyl derivatives and selctfluor or other fluorinating agents, do not work. Changes in the structures in formula (IV), including the different structures of the C and D rings recited in the claims, which take into account possible pharmaceutically useful structures, do not materially affect the diastereoselectivity of the silyl derivatives.

The specification provides examples of the process for producing a silyl derivative of formula (IV) as well as of its reaction with a fluorinating agent to obtain the compound of formula (I), with epoxy functionality in the C ring while referring to the starting material. The epoxy functionality in the C ring (second C structure) is the most unstable functionality under the reaction conditions as compared with other possible C ring structures (first, third and fourth structures) recited in the claims. The examples demonstrated that the claimed process could be conducted under the least advantageous conditions for reliable and effective production of 6a-fluorpregnanes of formula (I), with high yields, maximum stereoselectivity and minimum formation of by-products.

The specification also provides examples, e.g., example no. 4, of the process for producing a silyl derivative of formula (IV) as well as of its reaction with a fluorinating agent to

obtain the compound of formula (I), with double bond, not epoxy, functionality in the C ring while referring to the starting material.

The synthetic sequence from example no. 4 is shown in the following scheme:



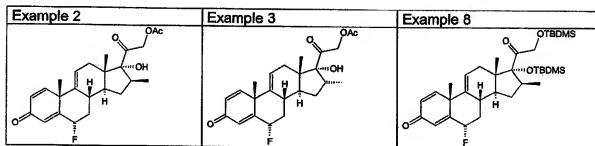
It is well known that different structures of the C ring type, such as those disclosed in the subject application, are easily interchangeable with one another. For example, starting from double bond in positions 9 and 11 (third C structure), epoxy can be easily obtained (second C structure). Starting from hydroxy derived in position 11 (fourth C structure), double bond can be obtained (first C structure). Starting from epoxy by the way of reduction, hydroxy in position 11 can be obtained.

Thus, in view of the disclosure in the present application, a person of ordinary skill in the art could readily practice the claimed process with all C ring structures, which include the most unstable epoxy structure as well as the more stable C ring structures, i.e., the first, third and fourth structures.

Similarly, a person of ordinary skill in the art could readily practice the claimed process with all D ring structures, particularly of the currently elected D ring structure of the formula:



The making and using of compounds having this D ring structure have been described and taught in the example nos. 2, 3 and 8 by the following structures:



Accordingly, a person skilled in the art, based on his/her knowledge and teachings from the specification and the specific examples disclosed therein, will be able to make and use the claimed invention as a whole, in its full scope, without any additional undue experimentation.

Accordingly, reconsideration and withdrawal of the rejection of claims 1-14 and 35-38 (in part) under 35 USC 112, first paragraph, for the lack of enablement are respectfully requested.

Restriction Requirement

In the Response to Remarks, the Examiner acknowledged Applicants' previous response to the restriction requirement. She indicated that the elected species is not a single compound, because it is unclear what Applicants meant by OP' and R4 at 16 and 17 positions, respectively, which includes hundreds of compounds. The Examiner stated that "species election was requested from the elected group to start the search and was not limited to species." The Examiner commented that Applicants' previous argument about the common property is not relevant, because the present application is not a national stage application.

Applicants respectfully seek clarification from the Examiner whether further species election is still required or was in fact withdrawn, in view of the substantive examination of the previously elected group and species and the pending office action as a result of the substantive examination. Applicants respectfully submit that there is no requirement that the species must be a single compound and that the Examiner has not provided any justification why a single compound must be elected as a single species.

In view of the Examiner's comments about Applicants' previous argument based on the common property, Applicants respectfully traverse the restriction requirement based on at least the following reasons.

Claim 35 refers to a **complete synthetic process** according to an embodiment of the present invention. The synthetic process comprises two steps:

the first step comprises the use of an unsaturated ketone as a starting material in order to obtain a silyl derivative of formula (IV); and

the second step comprises a reaction of a silyl derivative of formula (IV) with a fluorinating agent to obtain compounds fluorinated in the position 6 α , i.e. to obtain the compounds of general formula (I).

Claim 35 can be considered as a linking claim that connects all the inventions as disclosed:

claim 26 relates to the first step of the general process recited in claim 35, comprising the preparation of a silyl derivative of formula (IV) from a starting material, i.e., an unsaturated ketone;

claim 1 relates to the second step of the general process recited in claim 35, comprising a process for obtaining the compounds of general formula (I) by reacting the silyl derivative of formula (IV) with a fluorinating agent; and

claim 15 comprises silylated intermediates necessary and indispensable to perform the synthetic process as claimed. The intermediates are new and for the first time disclosed in the subject application.

As it can be clearly seen, the claimed process of synthesis comprises two essential elements:

- a) use of silyl derivatives of general formula (IV); and
- b) use of fluorine reagents of N-fluorosulfonimide- or N-fluorosulfonamide type.

Surprisingly it has been found by the Applicants, that other association different from the one as defined above does not result in the desired diastereoselectivity of the 6 α fluorinated derivatives.

Additionally, as stated above, different functionality of the steroid in the C and D rings does not affect the diastereoselectivity that can be achieved in the claimed reaction.

The factors having influence on diastereoselectivity are the following: stable silyl enol ether (compound IV), which withstands the fluorination conditions without breaking until the

fluorine atom has been introduced; and the election of gentle enough fluorine reagent, so that the silyl derivative does not break before introducing the fluorine.

With reference to Examiner's objections based on the MPEP § 806.05(f), Applicants would like to remark that the presently claimed **silyl derivatives of a compound (IV) are new**. The claimed **silyl derivatives** have not been disclosed in the prior art up to the filing date of the subject application. According to the present invention, the claimed **silyl derivatives** is mainly used to facilitate the introduction of a halogen atom, e.g., fluorine, the halogen of commercial and pharmacological interest when filing the subject application. Another and materially different process to obtain the claimed compounds as stated by the Examiner is not known. Because it cannot be demonstrated that that the product as claimed can be made by another materially different process (no support provided by the Examiner), the demanded scope of protection (claims 15-25 and 26-34) should be examined and considered allowable together.

With reference to the Examiner's objections based on the MPEP § 806.05(j), Applicants would like to remark that "Inventions of group V" **form an integral part of a general synthetic process as claimed in claims 35-38** ("Inventions VI to IX"). The claimed process of synthesis comprises two essential elements, as stated previously: a) use of silyl derivatives of general formula (IV) and b) use of fluorine reagents of N-fluorosulfonimide- or N-fluorosulfonamide type. In order to search and examine the claimed silyl derivatives of general formula (IV), the process for producing them must be searched and examined to ensure that the application is enabling. As it has been already shown, to obtain desired diastereoselectivity of the 6a fluorinated derivatives, especially produced intermediates will be used, the intermediates obtained by the process as claimed in claims 26-34, forming an integral part of a general synthetic process.

Applicants respectfully submit that the inventions of the groups VI, VII, VIII and IX, which comprise claims 1-14 and 35-38, where the C ring represents all of the claimed structures and D ring represents all of the claimed structures, particularly D ring has the second structure recited in the claims, are sufficiently disclosed in the specification and therefore patent protection with the present scope is fully justified.

Additionally, Applicants consider the inventions of the groups I-IV as totally related to the inventions VI-IX, because the silyl derivatives of a compound (IV) as claimed are

indispensable intermediates necessary to obtain the compounds of formula (I), as explained in detail above.

Accordingly, the argument that the inventions do not overlap in scope does not seem to find support on the present disclosure and on the teachings of the claimed invention. Applicants respectfully ask the Examiner to reconsider and withdraw the restriction and election of species requirement.

In the event that the restriction and election of species requirement is not withdrawn, Applicants hereby confirm the previous election of the invention of group VII, claims 1-14 and 35-38 where the C ring represents the second structure (epoxide), and the previous species election where the D ring represents the second structure having group R₄ in position 16 and group OP' in position 17.

Applicants appreciate the effort of the Examiner. An early Notice of Allowance with respect to all pending claims is respectfully requested. The Examiner is invited to contact Applicants' undersigned attorney by telephone to advance the prosecution.

Respectfully submitted,

JOSE VICENTE MURILLO GARRIDO *et al.*

June 3, 2009
(Date)

By: *V. Hsing* 53,128
for **WEIHONG HSING, PH.D.**

Registration No. 51,823

PANITCH SCHWARZE BELISARIO & NADEL LLP

One Commerce Square

2005 Market Street, Suite 2200

Philadelphia, PA 19103-7013

Telephone: 215-965-1200

Direct Dial: 215-965-1284

Facsimile: 215-965-1331

E-Mail: whsing@panitchlaw.com

WH/ml